CURRENT TOPIC

Reflections on measuring pain in infants: dissociation in responsive systems and "honest signalling"

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Consider the following scenario: Robert Smith R Barr is head nurse at a neonatal intensive care unit at a major teaching hospital; Joanne Johnston is the clinical director of the neonatology service. Both have been following closely the changing attitudes and published data on pain and stress in infants.[1] They believe that the formerly widely held assumptions that infants do not experience pain and do not benefit from analgesia are wrong. They now believe that premature infants not only have the neurological capability to experience pain, but that they may be hypersensitive to nociceptive stimuli,[2 3] and may remember pain experiences.[4] They are aware of the classic study by Anand and colleagues[5] and others since[6 7]supporting the idea that infants undergoing major painful operations will have better outcomes if given analgesics during surgery. Indeed, they have been active in a campaign to educate their colleagues that infants experience pain the way adults do. Many of their colleagues do not subscribe to this belief, which may partly explain why infants and children receive less analgesia for the same procedures than do adults.[8–13] Finally, they have instituted measures for "individualised, developmentally focused intensive care," where nursery routines and practices are organised to be as consistent as possible with the developmental strengths and vulnerabilities of premature infants.[14]

In pursuit of these aims, however, they have been trying to address the following question. What should be taken as evidence that the infant is in pain or stressed? This applies to premature infants undergoing repeated minor procedures some of which are painful and many of which are stressful, who are often recovering from major surgical procedures, and who may have chronic indwelling catheters, intravenous lines, etc. They recognise this poses a dilemma for several reasons. First, infants cannot tell us when they are experiencing pain the way older children and adults can. Second, they cannot make decisions as to when they could benefit from analgesia and activate their own patient controlled morphine analgesia units. And third, Robert's nursing colleagues, typically strong advocates of pain control in infants, are pushing for recognising crying and facial grimacing as signs of pain in infants, while Joanne's physician colleagues, sceptical of the non-specificity of behaviours as signs of pain, are pushing for physiological evidence of pain and stress before providing analgesia.

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The consultation

To help resolve this difference, they request a consult from Gerry, the child developmental psychologist. Child developmental psychologists have a long history of measuring stress in infants.[15] Robert and Joanne would like Gerry's help in understanding whether they should use behavioural measures, physiological measures, both or neither, to determine when to provide analgesia to their preterm infants. The catch is this: assuming that infants experience pain in the first place, it is no great insight to expect that infants will be experiencing pain when invasive procedures are taking place. The real question is how one determines that infants (and especially a particular infant) is in pain when no acute invasive procedure is taking place.

In preparation for the consultation, Gerry looked to see what had been reported about responses to pain and stress situations in infants. Among the many interesting things that Gerry found, three were particularly relevant. First, as expected, there were a wide variety of measures that had been used in infants.[1 16–18] All had strengths and weaknesses, and were variably difficult to obtain. However, they could be generally divided into overt or covert measures. Overt measures were usually behavioural, most commonly crying vocalisations, facial activity, and motor movements—components of which might be referred to as behavioural responsive systems. Covert measures were usually of physiological responsive systems of which there were many. The most common were heart rate (or heart period), vagal tone—a measure of heart rate variability—transcutaneous PO_2 and cortisol, the so-called stress hormone.

The second observation was that these measures were very non-specific, in the sense that both overt behavioural and covert physiological responses would occur in many non-pain contexts. This was especially likely if

one was interested in the infant's responses after the pain or stress stimulus had been removed—the very situation about which Gerry was being asked to consult. Thus, for example, there is a classic concatenation of facial features (mouth open, brow bulge, eyes closed, increased nasal–labial furrow) that is always there when a pain stimulus is applied.[16 19 20] However, it is also often present in many situations when an infant cries, such as when it is hungry.[21] Similarly, a spectrographic analysis of a pain cry often indicates features of a delayed onset, a prolonged expiratory phase, a higher pitch, and increased likelihood of disrupted harmonic structure (or dysphonation) when the stimulus is applied.[22 23] However, very soon after the pain stimulus is removed, the acoustic structure of the cry reverts to what is referred to as the basic, more rhythmical structure of the cry.[24 25] The non-specificity was equally true for the physiological measures, where almost any novel or often only mildly stressful stimulus situation could be reflected in changes in these systems.[26–28]

The third observation was perhaps even more problematic—namely, that behavioural indices of pain and stress were very loosely correlated and/or sometimes completely dissociated from physiological indices.[27] This was an interesting finding, because it has not widely been reported and is rarely the main point of the studies in which the dissociation was reported. However, it had come to Gerry's attention in several ways. Gerry happened to have attended the 1996 meeting of the International Society for Infant Studies in Providence, Rhode Island, in which a panel moderated by Megan Gunnar was entitled "Physiological measures in infant research: divining rod or Pandora's box." Its purpose was to reflect carefully on what we thought physiological measures were really contributing to our understanding of infant behaviour, especially when they do not agree with behavioural measures. The first speaker, Michael Lewis, noted that since he had been studying responsive systems in infants, one of the most robust findings was that the correlation between behavioural and physiological measures across situations and studies was about 0.3. These correlations were sometimes significant and sometimes not (often depending on sample size). However, the size of the correlations suggested that these physiological systems were only loosely, rather than closely, coupled to behavioural responsive systems.

Then there was the early report by Gunnar and colleagues in which they described behavioural and cortisol responses to circumcision in the presence or the absence of a pacifier.[29] They found that crying was reduced by about 40% when infants were given pacifiers, but there was no difference in cortisol concentrations after the surgery. Furthermore, crying during circumcision was not correlated with increases in cortisol in either the pacifier group or in the non-pacifier group. General motor activity was also reduced in the pacifier group. Consequently, the behaviour–physiology dissociation could not simply have been due to the pacifier being a competing response incompatible with crying. Given this dissociation between the behavioural and physiological measures, should we conclude that the intervention was, or was not, effective? In other words, should we take the behavioural measures as signs of pain (in which case the answer to the question of intervention would be "yes"), the physiological measures as signs of pain (in which case the answer would be "no"), or both (in which case the answer would probably be "we don't know").

A third report caught Gerry's eye. This was a study by White, *et al* (submitted) in which they examined stress responses to both a physical measurement (height and weight) exam and to a mock physical exam in infants with and without a clinically defined syndrome of colic. Even though these were not pain stimuli in any of the usual senses of the word, this study highlighted the problem of what should be taken as pain measures in a stressed infant in the absence of a clear stimulus. For one thing, both parents and many physicians think of, or classify, colic as a pain syndrome of infancy.[30 31] The pain—if that is what it is—is intermittent, recurrent, and presumably intestinally generated, rather than attributable to an acute procedure. Indeed, in considering the colic perplex, Barr et *al* had mused that infants with colic were the ultimate test case of our understanding of this infant experience. If we could ever really decide whether infants with colic were in pain, we would have achieved a real understanding of infant pain experience in general.[31] In fact, this made it much more like the situation on which Gerry was being asked to consult—namely, what should we take as signs of pain in infants who might be predisposed to recurrent painful events, were not undergoing acute painful procedures at the time, but in whom otherwise routine stresses were being encountered.

The results were no more comforting. For crying behaviour, the pattern of crying was the same for both groups—that is, there was more crying during the measurement and mock physical exams than at baseline or during the intervening break, and crying was greater among the colic infants, especially during the mock physical. For each of the heart rate, vagal tone, and cortisol responses, there were also significant responses to the interventions, but no differences between colic and non-colic groups. There was only one interaction suggesting higher heart rate in the colic subjects, and that was at the end during the mock exam. In summary, there was a fairly striking dissociation between behavioural and physiological measures to a typical set of stressful procedures. Although all measures were responsive, only the behavioural ones were differentially so.

Overall, Gerry's review of measures of pain and stress seemed to confirm a fairly basic principle—namely, that there was often a significant dissociation between overt behavioural and covert physiological measures used as indices of pain and stress. There was a second interesting trend: in most cases this dissociation suggested that the overt behavioural

measures were more likely than the covert physiological measures to be different between groups and/or more likely to be malleable to interventions.

The problem is not solved

It certainly looked like there was not going to be any simple answer to the question of how the neonatal intensive care unit staff were going to be able to tell when infants were in pain or distressed when the pain/stress stimulus was not present and only the behavioural or physiological responses were available for interpretation. Furthermore, it meant that there would be no easy resolution of differences of opinion as to when analgesia should be offered. On the one hand, some physicians or nurses could argue that behavioural responses that were not accompanied by physiological differences did not represent real signs of pain. Providing analgesia would overtreat these infants, increase the risk of undesirable side effects, and unnecessarily increase costs, to no one's benefit. On the other hand, other physicians or nurses could argue that behavioural differences were more sensitive than physiological measures. Consequently, relying on physiological differences would result in undertreating pain and stress in infants. Infants would be therapeutic orphans through no fault of their own, but because of the ignorance of adults who could not hear their pain language.

There was also the danger of a certain somewhat insidious bias sometimes found both in practice and in the published studies on pain and stress to believe that pain or stress occurs only when physiological measures show a difference. However, this bias, carefully examined, may be nothing but that: a reflection of a deeply held tendency to rank order our belief systems in terms of their closeness to some ideologically more basic or more scientific measure. As Robert Sapolsky notes in his book *The Trouble with Testosterone*,[32] this bias is a case of "what is often called physics envy, a disease that causes behavioural biologists to fear their discipline lacks the rigor of physiology, physiologists to wish for the techniques of biochemists, biochemists to covet the clarity of answers revealed by molecular geneticists, all the way down until you get to the physicists who confer only with god." If we put this bias aside, the data actually exacerbate rather than resolve the problem. They suggest that widely accepted response systems to pain stimuli do not act in accord with each other, but are, on the contrary, quite dissociable and dissociated.

A thought: honest signalling

Gerry was on the point of consulting with Robert and Joanne, but this observation about dissociated responsive systems continued to be bothersome. Gerry wished there was a way of making sense of this dissociation, in addition to noting that it was there. While pondering this question further, Gerry remembered some discussions about the concept of "honest signalling" from a previous course in evolutionary behavioural ecology. This wasn't exactly a clinical concept, but it seemed possible that it might have some relevance to the problem of "pain signalling" that was at stake here.

The concept of honest signalling arose in the context of the problem of sexual selection in evolutionary biology, and it was introduced to solve a dilemma in that field. From Darwin's time, evolutionary biologists had noted that several apparently exaggerated behavioural or physical traits (the peacock's plumage, or the tail of the long tailed widow bird,[33] for example) might well have been selected for, developed, and maintained because they would attract sexual partners. At the same time, however, many of these traits also carried significant costs in the currencies of evolutionary biology, such as increased energy expenditure or risk of predation. The dilemma was how to account for the apparent contradiction that females would be attracted to a male behaviour or physical trait that was a handicap for the male. To deal with this dilemma, Amotz Zahavi offered a proposal, which came to be known as "the handicap hypothesis." The proposal was that females prefer long tails (or other traits) precisely because they are handicaps.[34 35] Only the most fit can afford, so to speak, to have a long tail. As such, these traits act as reliable, or honest, signals of a male's fitness. In order for the handicap hypothesis to work in an evolutionary context, three conditions need to obtain: (i) that the signal be honest (in the case of mate selection, that there be a correlation between the trait and the individual's fitness); (ii) that the signals be costly; and (iii) that they be more costly for the less fit males.[36]

A corollary of this principle is that the signal need not be "honest" over the whole range of its possible manifestations. It will only be honest when the size of the trait (behavioural or physical) has a relatively high correlation with the genetic qualities of importance to the female (or the receiver). Furthermore, the range of "honesty" of the signal may be different for different signals. For example, fig 1 shows that the hypothesised signal A would only be "honest" over the highest range of the signal; the hypothesised signal B would be "honest" over a lower and greater range of the signal. A second corollary is that, if the sender can induce the receiver of the signal to respond in a similar way to a lower (or weaker) signal, then this "dishonest" signalling might result in even more benefit to the signaler, because the benefit would be received at less cost.

Even though the principle was delineated in regard to sexual selection, it may apply to biological signalling situations more generally.[36–38] One of the most interesting of these is that of signalling as a means of eliciting care giving responses and resources. Although it may seem counterintuitive at first, let us consider the speculative possibility that crying as a behaviour was selected for, not primarily as a sign of pain or distress, but rather as a signal of robustness and good health. From the evolutionary perspective, this would make sense. Most infant crying does not occur in response to specific pain situations. By far and away the most prevalent crying is non-specific and

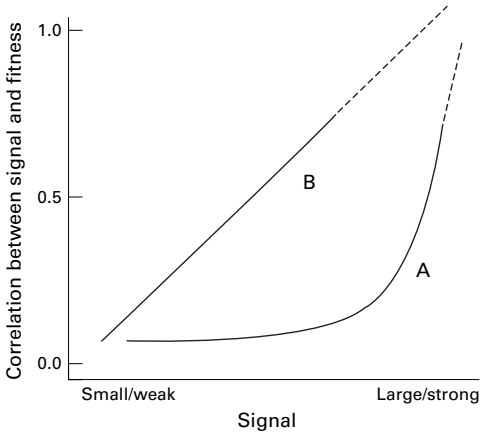

Figure 1 A and B represent two possible functions relating the size or strength of the signal to the strength of the correlation between the signal and the fitness of the organism. Hatched lines indicate range over which the signal is "honest."

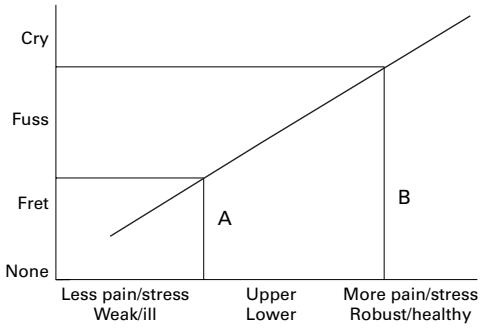

Figure 2 Upper X axis labels refer to the clinical assumption that more or louder crying is a sign of more pain or stress. Lower axis labels refer to the speculative evolutionary theory that more crying is an honest signal of robustness and health: A is an ill child; B is a healthy child.

seems to be clustered in the first few months of life, and which in the extreme is manifest as "colic."[39] Specifically from the point of view of the handicap hypothesis, this also makes sense. Crying compared with fussing, compared with intermittent frets, compared with quiet awake has relatively increased energy costs. Recently, Rao and colleagues documented an approximately 13% increase in energy cost during crying.[40] Furthermore, weak infants are not going to be able to mount a strong cry. They will probably cry less, or for shorter periods. For them, a long, loud cry is even more costly. Furthermore, if care givers can be persuaded to respond to fussing at a lower level than crying, then they will acquire resources even when the need signalled is not "honest." In short, crying might well function with the properties of an "honest signal" of good health in evolutionary terms.

If crying did develop to function as a signal of robustness rather than as a sign of pain and distress, what might the implications be for using crying behaviour as a sign of pain in the neonatal intensive care unit? One implication might well have importance for policies regarding distribution of care giving resources. Fig 2 shows an admittedly arbitrary linear function relating the infant condition (on the X axis) to the intensity of crying—represented as none, fret, fuss, cry—on the Y axis. However, the condition of the infant is represented in two ways. The upper X axis description tries to capture what is probably the most common assumption—that more or louder crying indicates more pain, stress, or illness. The lower X axis description tries to capture the speculation that crying in infants evolved as an "honest" signal of robustness and good health. In this case more or louder crying indicates robustness or health. The apparent irony is that, in the context of the neonatal intensive care unit, if the "intensity" of crying behaviour is taken to be the measure of pain and distress (and therefore the need for intervention), then the very infant that needs the support the most (infant "A") will be the one that gets the least, and vice versa. In short, acting on this assumption may actually compound the problem that we set out to solve.

Another implication could be that it provides a reasonable way to think of crying as a signal, rather than as a clinical sign, and why behavioural and physiological response measures might be dissociated. After all, evolution probably did not expect that we would have sophisticated cardiac or cortisol monitoring systems to "read" these physiological signs, so there would not be a lot of evolutionary pressure for them to become useful in persuading care givers to invest care and support. Most physiological responses are "covert" signals. However, crying and facial displays are "overt" signals, and are likely to be more effective in their function if they can persuade receivers of these signals to be responsive and supportive before they have to cry in extremis.

Submitting the consultation: what kind of response?

Gerry decided to amend the consultation report, and added these considerations about looking at behavioural measures and their dissociation from physiological measures in light of the notion of "honest signalling." The reason for including it was not that Gerry knew that these considerations were right. Indeed, Socrates' expression of self-doubt to Meno came to mind: "I shouldn't like to take my oath on the whole story".[41] The conceptualisation, after all, made several important, and perhaps wrong, assumptions about the evolution of crying behaviour and the shape of the function (fig 2) between robustness and crying, to mention just two. At the same time, these very uncertainties suggested interesting questions (such as the shape of the robustness-crying function) that might be turned into questions that could be addressed empirically. But perhaps most importantly, it underlined that the problem of pain measures in infants was much more complicated than it would seem, and that simplistic assumptions about what these measures tell us could do more harm than good. As a non-clinician, Gerry was not so sure the nurses and physicians, who understandably tended to be oriented to actions and decisions, would appreciate such uncertainty.

Both the nurses and physicians, however, did appreciate the consult despite the fact that it did not finally answer their question or resolve

differences of opinion as to what indices should be used as signs of pain. They were, after all, used to the special challenge that clinicians face, of acting in the absence of complete knowledge. Contrary to popular belief, they saw themselves more as reflective clinicians who were attracted by questions for which they did not have all the answers. Gerry's consult made it clear that their question was of fundamental importance for at least four professions, for infants and children everywhere, for our understanding of human nature, and for both theory and practice. There was clearly some important work to do. Trying to understand pain measurement in infants was a pretty good place to be doing it.

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